

A BULL IN A PILL SHOP: ALPHA-GAL ALLERGY COMPLICATING TREATMENT OPTIONS FOR POSTPROCEDURAL HYPOTHYROIDISM

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ABSTRACT

Objective: The galactose-alpha-1,3-galactose (alpha-gal) allergy, an IgE-mediated response to nonprimate meat, has a singular pathogenesis linked to tick bites and a delayed allergic presentation, which makes it especially cumbersome to diagnose and manage. As a large array of enteral medications contain ingredients derived from meat byproducts, this can affect the care of alpha-gal patients across multiple medical disciplines. Our objective is to present a patient with an alpha-gal allergy, which can complicate hypothyroidism treatment selection.

Methods: In this case of difficulty tailoring thyroid replacement therapy secondary to the alpha-gal allergy, the diagnostic studies included IgE immunoassays for alpha-gal as well as thyroid function tests.

Results: A 45-year-old woman with postoperative hypothyroidism and a history of an alpha-gal allergy (diagnosed after an anaphylactic reaction to beef) could not be immediately started on any common thyroid hormone replacement formulation because of our concern regarding the possible presence of nonprimate mammalian meat

byproduct components in the thyroid hormone medication. After consulting allergy and immunology specialists and compounding pharmacists and contacting multiple drug companies in an effort to confirm the nature of the inactive ingredients in their thyroid hormone products, she was prescribed a plant-based compounded levothyroxine preparation with good clinical results.

Conclusion: This case emphasizes the importance of recognizing various risk factors and common drugs which may be associated with the alpha-gal allergy. It is not known how to best tailor enteral medications for patients with an alpha-gal allergy. Further research and pharmaceutical attention to this allergy are needed. (AACE Clinical Case Rep. 2020;6:e101-e104)

Abbreviations:

alpha-gal = galactose-alpha-1,3-galactose; **TSH** = thyroid-stimulating hormone

INTRODUCTION

The IgE-mediated allergy to galactose-alpha-1,3-galactose (alpha-gal), a carbohydrate expressed on nonprimate mammalian proteins, has gained more clinical significance as it can present with serious, potentially fatal reactions (1). In general, recognizing a specific allergy is the first step in prescribing avoidance; but with delayed symptoms, uncertain prevalence, and an unclear diagnostic approach, alpha-gal allergies are difficult to recognize and prevent (2). To further complicate the clinical picture, some patients can tolerate small portions of nonprimate mammalian meat or tolerate one kind of meat over another (1).

This recurrent, potentially life-threatening allergic reaction to meat is primarily linked to tick bites (2). Urticaria, angioedema, or anaphylaxis were the

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most common presentations in initial reporting (3), but esophagitis and/or gastroenteritis exclusively have also been documented (1). Not only do some patients develop atypical allergic reaction signs, the onset of symptoms can be significantly delayed compared with typical IgE-mediated reactions, sometimes 3 to 6 hours after meat consumption (4).

Commercially available levothyroxine, liothyronine, combination, and desiccated thyroid formulations, whether brand name, generic, tablet, soft gel capsule, or liquid, can contain meat byproducts with few exceptions. This can be a concern for anaphylaxis or angioedema if one has an alpha-gal allergy (Table 1) (5,6). Any medication that includes any natural, nonprimate thyroid extract as an active ingredient is at risk for having the alpha-gal moiety. It has been shown that alpha-gal is prominently present on mammalian thyroglobulin (7). Inactive ingredients, specifically magnesium stearate and gelatin, can be derived from a nonprimate, meat-based source (8), and other bovine-derived products, such as heavy cream, have been shown to contain detectable amounts of alpha-gal (9). There is 1 reported case of highly suspected reactions to magnesium stearate in several enteral medications (8). Of note, this is the only other article to study this allergy in a patient receiving enteral medications. To date, there have been no reports of alpha-gal allergic reactions provoked by thyroid hormone supplements.

Alpha-gal allergy patients can have delayed reactions to a variety of nonprimate mammalian meat, but can also have cross-reactivity to medications and medical supplies that contain meat byproducts, which is an understudied potential source of iatrogenic anaphylaxis. Our objective was to report a patient in whom there were concerns regarding the correct choice of a L-thyroxine treatment preparation because of the history of an anaphylactic reaction related to alpha-gal allergy, and to describe the therapeutic approach taken.

CASE REPORT

A 45-year-old woman with a history of an alpha-gal allergy and follicular thyroid neoplasm status post right hemithyroidectomy presented with postoperative hypothyroidism. Before the hemithyroidectomy surgery, she was diagnosed with an alpha-gal allergy via elevated alpha-gal IgE of 122.40 IU/mL (normal, <0.10 IU/mL) after having an anaphylactic reaction to beef and a concern for dairy intolerance. All of these occurred after she sustained a bite from the *Amblyomma americanum* tick. After the hemithyroidectomy surgery, the patient was diagnosed with noninvasive follicular thyroid neoplasm with papillary-like nuclear features, and her serum thyroid-stimulating hormone (TSH) levels ranged between 5 to 6 μ IU/mL (not on thyroid replacement). The goal was to prescribe thyroid

Table 1
Thyroid Hormone Formulations and Potential Ingredients That Could Contain Animal Byproducts

Thyroid hormone formulations	Company name	Potential source of animal byproduct
Synthetic T4		
Synthroid TM	AbbVie	Magnesium stearate, lactose monohydrate (5) ^a
Levothyroxine (authorized generic)	Bryant Ranch Prepack	Magnesium stearate (5)
Levoxyl TM	Pfizer	Magnesium stearate (5)
Levothroid TM	Physicians Total Care	Magnesium stearate (5)
Euthyrox TM	Provell Pharmaceuticals	Magnesium stearate, gelatin (5)
Tirosint TM	IBSA Pharma	Gelatin (5)
Synthetic T3		
Liothyronine sodium (authorized generic)	Greenstone	Gelatin (5)
Cytomel TM	Pfizer	Gelatin (5)
Triostat ^{TM,b}	Par Pharmaceutical	Animal thyroid extract (5)
Combo of synthetic T3 and T4		
Thyrolar TM	Allergan	Magnesium stearate and gelatin (5)
Desiccated thyroid extracts		
Armour thyroid TM	Allergan	Animal thyroid extract (5)
Nature-Throid TM	RLC Labs	Animal thyroid extract, magnesium stearate, lactose monohydrate (6)

Abbreviations: T3 = triiodothyronine; T4 = thyroxine.

^aNumbers in brackets refer to references listed at the end of the manuscript.

^bStrictly parenteral option.

hormone replacement to initiate a cancer-suppressive strategy. The American Thyroid Association recommends a serum TSH of 0.5 to 2 μ U/mL in low risk thyroid cancer patients postoperatively (10). The standard treatment of choice for correcting hypothyroidism is synthetic thyroxine (levothyroxine).

Because of the possible reactions with all common formulations of thyroid hormone replacement in this patient, choosing a safe option was complicated and involved a multidisciplinary team, including allergy and immunology specialists and compounding pharmacy consultants. Inactive ingredients were the most common concern when choosing a thyroid hormone replacement, specifically magnesium stearate, gelatin, and lactose. Three pharmaceutical companies were contacted to confirm the origins of the magnesium stearate and/or gelatin based on the hospital's formulary: AbbVie, Pfizer, and Mylan (see Table 1). Neither AbbVie nor Pfizer were able to give more information or could not guarantee that the inactive ingredients were plant-derived. Daily or weekly parenteral synthetic thyroid hormone therapy was considered; however, it was not feasible for the patient. She was eventually prescribed pure, pharmaceutical-grade levothyroxine with a plant-based filler, vegetarian capsule, and magnesium stearate derived from vegetable sources. The initial dose was 25 mcg daily. She tolerated this compounded levothyroxine preparation well without any adverse reactions, and the TSH goal was achieved.

DISCUSSION

The risk factors predisposing a patient to an alpha-gal allergy are detailed in Table 2 (2,3,4,9,11,12). After the reaction was first noted in patients treated with cetuximab, which has an alpha-gal epitope on the antigen-binding fragment, various tick bites in multiple geographic areas were described as the most probable significant risk factor for the alpha-gal allergy (2-4). The alpha-gal epitope has been localized to the gastrointestinal tract of *Ixodes ricinus* (3). But as there are many individuals who have IgE directed against alpha-gal and no clinically significant meat allergies (4), other potential risk factors have been studied. The alpha-gal epitope is structurally similar to the blood group B antigen, and there is strong evidence that having blood type B appears to be protective (11,12). Lastly, even though allergic responses to gelatin (derived from mammalian collagen) and dairy products are heterogeneous, alpha-gal has been detected in gelatin and milk products (9).

Alpha-gal allergy has been associated with other medications and medical products, besides thyroid replacement medications (Table 3) (13-19). The correct diagnosis of an alpha-gal allergy starts with a good history; making sure to ask about tick exposure and delayed reactions to nonprimate mammalian meat, gelatin injections, or heavy creams, and then likely includes an anti-alpha-gal IgE

immunoassay and/or skin prick testing (15). Although the alpha-gal allergy was initially described as a red meat food allergy in 2009, we now know the alpha-gal moiety can be found in other mammalian-derived foods, medications, and medical devices.

Cetuximab was the first medication to be investigated because it caused a rapid reaction (likely because it is intravenously administered) in subjects that had IgE antibodies against alpha-gal (13). Even though heparin is widely used and is made from porcine or bovine tissue that is likely high in alpha-gal content, there are relatively few reports of reactions to heparin among alpha-gal sensitized subjects (14). But as in the current patient, medical care can be delayed or recommended against in alpha-gal patients based largely on case reports that build a strong case for association, but cannot show complete causality (17). Also, the theoretical risk is not just allergic reactions (i.e., urticarial, anaphylaxis, or angioedema); there is concern that patients unknowingly sensitized to alpha-gal could develop premature bioprosthetic (i.e., porcine or bovine) heart valve failure after replacement (18).

We do not have an extensive list of medications and medical products that contain meat byproducts or the alpha-gal carbohydrate moiety. And while physicians can

Table 2
Risk Factors Associated with
Acquiring Meat Allergy as an Adult

Multiple tick bites (2) ^a
<i>Ixodes ricinus</i> and <i>Ixodes holocyclus</i> tick bite(s) (3)
<i>Amblyomma americanum</i> tick bite(s) (4)
Gelatin allergy (9)
Milk allergy (9)
A and O blood groups (11,12)
^a Numbers in brackets refer to references listed at the end of the manuscript.

Table 3
Common Drugs/Agents
Associated with Alpha-Gal Allergy Reactions

Cetuximab (13) ^a
Heparin (14)
Intravenous colloids (15)
Vaccinations, specifically MMR, varicella, DTaP, DTaP/IPV, and live attenuated herpes zoster (16,17)
Prosthetic heart valves that are animal derived (18)
Antivenom (19)
Abbreviations: DTaP = diphtheria, tetanus, and pertussis; DTaP/IPV = diphtheria, tetanus, and pertussis, and polio; MMR = measles, mumps, and rubella.
^a Numbers in brackets refer to references listed at the end of the manuscript.

prescribe avoidance of meat ingestion to our patients, we are also at risk of prescribing medications that can put patients at risk. For instance, magnesium stearate and gelatin are found in formulations of acetaminophen, naproxen, lisinopril, clonidine, and hydrocodone, and allergic reactions to these medications have been potentially linked to alpha-gal. Pharmaceutical manufacturers do not test for the alpha-gal moiety; and the Food and Drug Administration does not require pharmaceutical companies to report information on inactive ingredients in package inserts (8). For us to verify plant versus mammalian byproduct information, we had to work with allergy and immunology physicians and compounding pharmacists as well as contact multiple manufacturers directly, which caused a delay in thyroid hormone replacement after thyroidectomy. Table 1 also demonstrates the diversity of manufacturers that produce thyroid hormone replacements.

Lastly, this is a patient that had many risk factors for the alpha-gal allergy even before her diagnosis: O blood group, multiple allergies (including gelatin), a history of multiple tick bites (including *Amblyomma americanum* exposure), and a history of anaphylactic reactions. This is the type of patient that could most benefit from increased research and more detailed guidelines and pharmaceutical attention to this allergy.

CONCLUSION

Our case emphasizes how much this allergy can affect the treatment of a common endocrinopathy. It is essential to diagnose the alpha-gal allergy early in our patients and manage appropriately. This requires a multidisciplinary collaboration in healthcare in order to find the best therapy for these patients to avoid severe adverse effects. Gaining a better understanding of the prevalence and diagnostic and therapeutic approach would not only help clinicians treat this patient population, but it would also help standardize and refine medication development and prescription choice.

DISCLOSURE

The authors have no multiplicity of interest to disclose. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or the United States Government.

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